CHAPTER I. INTRODUCTION

1.1 Background

Osteoporosis is a bone disease characterized by a decrease in bone mass and damage to the microarchitecture of bone tissue (Morin et al., 2023). The World Health Organization (WHO) defines osteoporosis as a progressive systemic skeletal disease with consequent increased bone fragility and susceptibility to fractures (Noh et al., 2020). Osteoporosis is a bone disease whose global prevalence reaches 18.3%, affecting approximately 1.36 billion people out of the 7.9 billion global population (Salari et al., 2021). The results of research by the Indonesian Osteoporosis Association (PEROSI) and the White Paper report that the prevalence of osteoporosis in women over 50 ranges from 23% to 53%. At the same time, in men, it is lower at around 10%-27%. The fracture risk due to osteoporosis is estimated at around 40%-50% in women and 13%-22% in men (Kemenkes, 2020). The causes of osteoporosis are multifactorial, including aging, menopause, endocrine disorders, physical activity levels, and side effects of certain drugs that vary depending on the type of osteoporosis (Sozen et al., 2017).

Osteoporosis is classified into primary osteoporosis, which includes postmenopausal osteoporosis, and secondary osteoporosis, which is caused by the use of drugs such as glucocorticoids (Akkawi & Zmerly, 2018). Glucocorticoids are widely used to treat various inflammatory, immunologic, and allergic disorders. However, long-term or high-dose use of glucocorticoids will lead to decreased bone formation and increased bone resorption. Excessive bone resorption results in bone thinning and widening of the bone medullary cavity, which triggers osteoporosis.

Osteoporosis caused by glucocorticoids is known as Glucocorticoid-Induced Osteoporosis (Yu et al., 2014). Glucocorticoids induce apoptosis of osteoblasts and osteocytes and disrupt the osteocyte lacuna-canalicular network, ultimately reducing bone quality (Gado et al., 2022). The research of Weinstein et al. (2017) proved that the administration of glucocorticoid drugs for 14 days showed a decrease in the number of osteoblasts and an increase in the number of osteoclasts. According to Johnson et al. (2022), the most common and frequently used glucocorticoid type is dexamethasone, a drug with potent anti-inflammatory effects. In their study, Laswati et al. (2015) showed that the administration of dexamethasone at a dose of 0.1 mg/kg body weight can induce osteoporosis in rats.

Several therapeutic options for osteoporosis exist, including bisphosphonates, calcitonin, anabolic agents like calcium and vitamin D, selective estrogen receptor modulators (SERMs), tibolone, and teriparatide (Tu et al., 2018). However, while these drugs offer beneficial effects on osteoporosis, they also carry various side effects (Khosla & Hofbauer, 2017). For instance, bisphosphonates and denosumab have been linked to osteonecrosis of the jaw, atypical femoral fractures, atrial fibrillation, and kidney damage (Boonen et al., 2012). Excessive use of bone-promoting agents such as fluoride can lead to calcium accumulation and poor bone mineralization (Sun et al., 2020). Oral gavage of the selective estrogen receptor modulator, raloxifene, for 28 days did not significantly improve bone strength (Folwarczna et al., 2007). Teriparatide therapy is associated with high costs and requires daily injections. The positive effects of this therapy tend to decline rapidly after treatment discontinuation (Black & Rosen, 2016).

The duration of osteoporosis medication can range from 12 to 36 months (Black et al., 2012). Bisphosphonates like alendronate sodium require 6 months (180 days) to increase and restore bone strength to normal levels significantly (Ozsahin et al., 2017). Injections of parathyroid hormone analog drugs take 12 weeks (84 days) to increase and restore bone strength to normal levels significantly (Wang et al., 2022). Additionally, some drugs have overlapping indications, and it is important to note that not all osteoporosis medications are approved by the Food and Drug Administration (FDA) for treating osteoporosis (Tu et al., 2018). Therefore, developing new and effective therapies for treatment with fewer or no side effects is necessary.

Various studies suggest that combinations of natural plant extracts have greater potential as alternative medicines (Lee et al., 2017). Molecules extracted from natural compounds possess high anti-inflammatory, antioxidant, and regenerative effects, justifying the successful use of these products in various diseases (Arulselvan et al., 2016). In osteoporosis research, various plant extracts have been explored. Among them, Saleh et al. (2024) found osteoprotective potential from combining *Cichorium intybus* L. root extract and *Portulaca oleracea* L. leaf extract in suppressing bone resorption and stimulating bone formation in osteoporotic rats. Badary et al. (2022) used olive oil extract and *Lepidium sativum*, which, with their high flavonoid and calcium content, were able to repair and increase cortical thickness in dexamethasone-induced rats. Laswati et al. (2015) demonstrated that *Spilanthes acmella* extract significantly increased the number of osteoblast cells. According to Sromova et al. (2023), osteoblast cells synthesize bone extracellular matrix (ECM) components like collagen and chondroid matrix, which function in bone formation, mineralization, and provide structural support.

Beyond terrestrial plant extracts, marine resources like algae are also being investigated as therapeutic candidates for osteoporosis. Studies have demonstrated their benefits, both as food and supplements, for disease prevention and health maintenance (Ganesan et al., 2019). *Sargassum* is a brown alga that contains various nutritionally important organic compounds and exhibits bioactive properties (Lafarga et al., 2020). Diverse secondary metabolites found in *Sargassum*, including steroids, tannins, saponins, flavonoids, terpenoids, glycosides, fucoidans, and phenolic compounds, possess potential as anti-osteoporosis agents (Nazarudin et al., 2021). *Sargassum*, belonging to the phylum Phaeophyta, is among the most extensively studied about cancer (40%), diabetes (85%), arthritis (67%), neurodegenerative diseases (71%), obesity (59%), osteoporosis (46%), liver disease (80%), and cardiovascular disease (84%) (Meinita et al., 2022).

According Lu et al. (2019) that fucoidan extract from *Sargassum hemiphyllum* could prevent osteoclast differentiation and bone loss *in vitro*. Furthermore, Yamaguchi (2024) found that compounds from *Sargassum horneri* extract can stimulate osteoblastogenesis and inhibit osteoclastogenesis *in vitro*. Additionally, Wu et al. (2019) showed that administering *Sargassum integerrimum* extract at a dose of 350 mg/kg body weight to an ovariectomy (OVX)-induced osteoporosis rat model significantly improved femoral bone mineral density (BMD), enhanced bone biomechanical properties, and improved bone microstructure.

Research on utilizing brown algae (*Sargassum*) as a nutraceutical product is still in its early stages, with most studies conducted *in vitro* (Meinita et al., 2021). The limited number of *in vivo* studies and the scarcity of research on the anti-osteoporosis potential of *Sargassum* extract in dexamethasone-induced osteoporosis rat models

highlight the critical need for further investigation. It is hoped that the findings from this research can serve as a candidate for future osteoporosis therapy.

1.2 Problem Formulation

Based on the above background, the formulation of this research problem is as follows:

1. Identify bioactive compound profiles that have potential as antiosteoporotic from brown algae extract (*Sargassum crassifolium*).
2. What is the effect of brown algae extract (*Sargassum crassifolium*) on the improvement of bone histomorphometry in osteoporotic rats?
3. What is the effect of brown algae extract (*Sargassum crassifolium*) on the improvement of bone extracellular matrix in osteoporotic rats?
4. What is the effect of brown algae extract (*Sargassum crassifolium*) on body weight changes in osteoporotic rats?

1.3 Research Purpose

The objectives of this research are:

1. To identify the profile of bioactive compounds with potential antiosteoporotic activities from brown algae extract (*Sargassum crassifolium*).
2. To determine the effect of brown algae extract (*Sargassum crassifolium*) on the improvement of bone histomorphometry in osteoporotic rats.
3. To determine the effect of brown algae extract (*Sargassum crassifolium*) on the improvement of bone extracellular matrix in osteoporotic rats.
4. To determine the effect of brown algae extract (*Sargassum crassifolium*) on body weight changes in osteoporotic rats.

1.4 Benefits

This research provides additional insights and serves as a source of information in the field of medicinal plant pharmacology, particularly regarding the use of brown algae (*Sargassum crassifolium*) to address bone loss due to osteoporosis. It also offers an effective alternative therapy to chemical drugs currently available in the community. This research is expected to assist the government in addressing osteoporosis-related issues in Indonesia and can potentially be further developed into basic food ingredients and functional supplements.